

REMARKS

Applicants would like to thank Examiner Steadman for the helpful discussion with of the issues in the telephone conference on July 28, 2009 with Applicants' representative. During the discussion, prospective amendments to address the various bases for the Examiner's rejections were discussed. In light of this discussion, Applicants have incorporated some of the amendments suggested by the Examiner.

Status of the Claims

Claims 1, 6, 7, 12, and 14-16 are currently pending and under examination. Claims 2-5, 8-11, 13, 17, and 18 have been canceled without prejudice or disclaimer of the subject matter claimed therein. Claim 19 is new. The pending claims are allowable for the reasons noted below and otherwise of record.

Amendments to the Claims

Claims 1 has been amended. Representative support for the amendment to claim 1 can be found at page 3, line 31 to page 4, line 5; page 9, lines 10-21; Table 1 on page 22; and, Table 4 on page 32.

Claims 6 and 7 have been amended. Representative support can be found in claims 1, 6, and 7 as originally filed.

Claims 14 and 15 have been amended. Representative support can be found at page 9, lines 10-21.

Claim 16 has been amended. Representative support can be found at page 9, lines 10-21.

Claim 19 is new. Representative support can be found in claims 1, 6, 7, and 9 as originally filed, and at page 9, lines 10-21.

The amendments to the claims and the addition of claim 19 do not introduce prohibited new matter.

Claim Objections

Claim 9 is objected to for allegedly failing to narrow the scope of claim 1, from which claim 9 depends.

Without acquiescing to the merits of the objection, Applicants have canceled claim 9. It is therefore respectfully requested that this objection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 17 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Office Action alleges that claim 17 is indefinite in that the preamble recites a broader limitation than the narrow limitation described in the claimed method. Without acquiescing to the merits of this rejection, Applicants have canceled claim 17. It is therefore respectfully requested that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

A. Claims 1, 6-7, 9, 12, and 14-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action alleges that the claims use of the term “homology” as recited in the claims may refer to both “identity” and “similarity.” Without acquiescing to the merits of the rejection, Applicants have amended claim 1. Applicants therefore respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

B. Claims 1, 6-7, 9, 12, 14, and 15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable the claimed invention.

The Office Action alleges that the specification fails to enable producing any type III AFP polypeptide using any yeast host deficient in protein glycosylation. Moreover, the Office Action alleges that recitation of the term “homology” may refer to both “identity” and “similarity.” As discussed above, the claims have been amended to recite that the AFP have identity to SEQ ID NO: 1.

The Office Action also alleges that the claims are unlimited in how pmt1 and/or pmt2 deficiency is achieved. The Office Action further alleges that the claims may further encompass glycosylation deficiency through non-disclosed measures.

Without acquiescing to the merits of the rejection, Applicants have amended claim 1.

With respect to the Office Action's comments on how pmt1 and/or pmt2 deficiency is achieved, it is submitted that any method known in the art would suffice, so long as the host cell becomes deficient in pmt1 and/or pmt2. It may be through processes such as deletion of the genes expressing it, suppression of its expression, or degradation of the mRNA encoding the protein. All such methods would work with the claimed invention and would be readily apparent to one skilled in the art. Applicants respectfully point out that mutant cells deficient in pmt1 and/or pmt2 are well known in the art and such mutants are known to be incapable of glycosylating their particular substrates. Furthermore, no undue experimentation would be required, as long as the pmt1 and/or pmt2 are deficient from the host cell. It is therefore respectfully requested that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 6, 7, 9, 12, and 14-17 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious under Chapman (WO 97/02343) ("Chapman") in view of Ng (U.S. Patent Application Publication 2002/0068325) ("Ng") and Gentzsch (FEBS Lett 377: 128-130, 1995) ("Gentzsch 1").

The Office Action alleges that Chapman discloses a recombinant type III AFP HPLC-12 produced in *Saccharomyces cerevisiae*, that Ng discloses O-linked glycosylation in the ER by pmts, and that Gentzsch 1 discloses pmt1 and pmt2 deletion mutants. The Office Action alleges that it would be obvious to recombinantly produce the AFP of Chapman in the pmt mutants of Gentzsch 1 given the disclosure concerning glycosylation disclosed by Ng.

Chapman discloses a production of a type III AFP HPLC-12 produced in *S. cerevisiae*. As previously stated, Chapman discloses that the AFP is properly produced and secreted in a wild-type yeast. Ng discloses the use of pmt mutants as a means to overcome "aberrant" glycosylation that leads to rapid degradation of the recombinant protein (*see* Ng at paragraph [0071]). Ng suggests the use of a glycosylation deficient yeast if the desired protein is not being secreted properly. The aberrant glycosylation disclosed by Ng prohibits proper folding of the recombinant protein and thus the protein is not secreted and is rapidly degraded.

The AFP disclosed by Chapman, however, is reportedly produced efficiently and is secreted in wild type yeast.

Attached to this document is a Declaration by Dr. Chapman, an inventor of the present invention and an inventor of the cited "Chapman" reference that states the reason that the cited references would not render the claimed invention obvious. The attached Declaration of Dr. Chapman describes three particular reasons that one skilled in the art would have no reason to combine the cited references to arrive at the claimed invention. Those reasons are elaborated herein:

1. At the time of the present invention, one skilled in the art could not predict which enzymes would be responsible for glycosylating the type III AFP. The Declaration of Dr. Chapman refers to a reference of Gentzsch (Glycobiology 7: 481-486, 1997) ("Gentzsch 2"). the author of Gentzsch 2 is the same as that of the cited Gentzsch 1 reference. Gentzsch 2 discusses the problems in attempting to manipulate the glycosylation of a protein in yeast. Gentzsch 2 discloses that the selection of one particular pmt enzyme is often ineffective in manipulating the glycosylation, and often 2 or 3 pmt enzymes will have to be affected. Moreover, the Gentzsch 2 reference discloses that there is no way of predicting which pmt enzyme or combination of enzymes needs to be targeted for manipulating the glycosylation of a desired protein.

2. At the time of the present invention, it had further been demonstrated that glycosylation has no affect on the activity of AFP in rye grass. The attached reference of Pudney (Archives of Biochemistry and Biophysics 410: 238-245, 2003) demonstrate that modulating the glycosylation of AFP in rye grass had no effect on the functional activity of the AFP. Accordingly, one skilled in the art would interpret this to indicate that glycosylation is not a significant factor in the successful production and function of AFP.

3. At the time of the present invention, it was also unknown what effect glycosylation would have on a protein expressed in yeast. While Ng discloses that decreasing glycosylation may correct for proteins that are suffering from mis-folding and not being secreted properly, there were conflicting reports as to how glycosylation might affect a protein. The attached reference of Sanders (J. Cell Biol. 145: 1177-1188, 1999) discloses that glycosylation of a protein is required for the stability and function of a protein produced in yeast. Accordingly, one skilled in the art would not have expected that decreasing the glycosylation of AFP would improve the functional activity of the AFP.

Moreover, Applicants point out that the AFP disclosed by Chapman is successfully

secreted and functional when produced in wild-type yeast. Thus, particularly based on the disclosures of Pudney and Sanders, one skilled in the art would expect that glycosylation was either required or of no import to the production and function of the AFP. Further, one skilled in the art would be inclined to dismiss the Ng reference for at least two particular reasons: 1) Ng discloses that modulating glycosylation is useful if the protein is experiencing mis-folding in yeast, and as Chapman demonstrates, that was not the case with the type III AFP; and 2) it was known in the art that modulating the glycosylation of a protein exerted unpredictable effects.

It is therefore submitted that one skilled in the art could not have arrived at the claimed invention based on the references of Chapman, Ng and Gentsch 1. The references of Pudney and Chapman demonstrate that glycosylated AFP function perfectly well. The reference of Ng would therefore appear not to be applicable to the AFP as the protein was already reported to be properly secreted and to properly function in yeast. Moreover, AFPs had been reported to be unaffected by glycosylation. Further, one skilled in the art would not know which enzymes to target in yeast to affect the glycosylation. Accordingly, the claimed invention is unexpected and surprising in the art. It is therefore respectfully requested that this rejection be withdrawn.

Double-Patenting

Claims 1, 6-7, 8, 12, and 14-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of US Patent 7,297,516 in view of Ng and Gentsch 1.

US Patent 7,297,516 is the patent issued from the US national stage application of Chapman. The deficiencies of Chapman, Ng, and Gentsch 1 are discussed above. Accordingly, for the same reasons as discussed above, it is submitted that the claimed invention is not obvious over these cited references. It is therefore respectfully requested that this rejection be withdrawn.

Conclusion

The foregoing amendments and remarks are thought to obviate the basis for the Examiner's rejections and to otherwise place the application in condition for allowance. Accordingly, Applicants respectfully request reconsideration and allowance of the pending claims. Should an interview be helpful to further prosecution of this application, the Examiner is

invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: **October 6, 2009**
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Respectfully submitted,
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